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Disseminating a Free, Practical Java Tool To Interactively Generate and Edit 2D Chemical Structures

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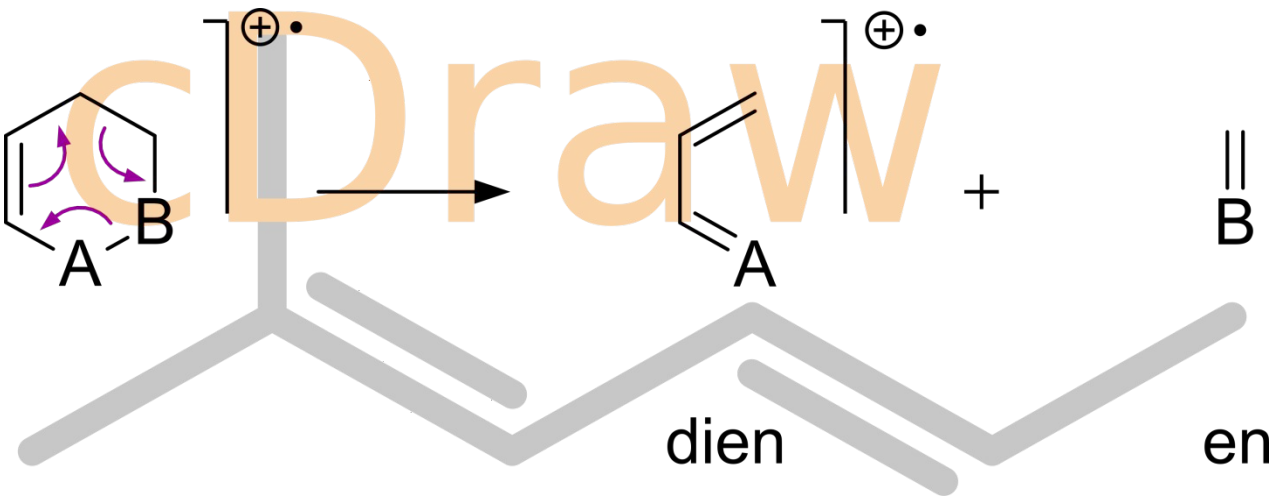
ABSTRACT

The interactive generation of chemical structure diagrams is an integral activity in the study of chemistry as well as in professional chemistry environments. For educational purposes, in particular, the existence of suitable software tools free of charge is of great importance. Albeit a number of free chemical drawing applications are currently available, there are often limitations as to the included basic drawing tools, ease of handling and installation, or time limits of free access. The Java desktop application cDraw is an interactive chemical drawing software for generation of publication-quality figures. The user interface has been designed with a clear focus on intuitive and convenient handling, and currently is offered in nine languages. The software allows drawing of 2D chemical structure diagrams using a basic set of built-in templates and bond generation mechanisms. Drawings can be exported as EPS, PDF, PNG, SVG, and TIFF images or copied through the clipboard. cDraw sessions can be stored in the XML-based CDML file format; additionally, there are basic import/export capabilities for the popular CDXML, CML, and SDF file formats. Molecules can be inserted using line notation (InChI, MCDL, and SMILES) and molecular meta information such as IUPAC name and Chemical Abstract Service number can be obtained from drawings via online NIH CACTUS queries. Due to multilanguage support and an intuitive user interface, the software should especially appeal to students in secondary and tertiary education.



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High School/Introductory Chemistry, First-Year Undergraduate/General, Second-Year Undergraduate, Upper-Division Undergraduate, Graduate Education/Research, Chemoinformatics, Communication/Writing, Molecular Properties/Structure, Undergraduate Research, Descriptive Chemistry

INTRODUCTION

Visualization and the understanding of spatial relationships of molecules are of paramount importance in chemistry and its neighboring disciplines. As such, visuospatial skills constitute a central component of teaching and learning, and their substantial effect on student success and retention has been recognized.[1,2] More recently, ubiquitously required skills subsumed under the term visual literacy have been defined as a so-called threshold concept for biochemical disciplines and the need for explicit inclusion of relevant instruction modules has been highlighted.[3]

Contemporary molecular visualization is heavily dependent on software, and students thus not only need to master the fundamental chemical concepts defining molecular structure, but also have access to and be able to operate relevant visualisation software. For beginners, chemical concepts as well as software availability and handling are unique elements, and their simultaneous mastering can often lead to cognitive overload.[4] It has thus been recognized that digital resources such as relevant software can help introduce core concepts in lectures and aid students in the mastering of subject areas that require the use of new terminology; importantly, the design of the software should consider the difficulty of extracting new information and minimize such efforts as far as possible.[5]

Our own experiences as teaching practitioners support those findings, with students commonly unable to transfer their experience of common digital metaphors from one platform or application to another. Albeit often referred to as the generation of the “digital natives”,[6] it has become clear that the mere exposure to technology does not result in the ability to use it. While it was initially assumed that people born in times of widespread use of digital technology (i.e., after 1980, “digital natives”) intuitively know how to use technology, later and more recent appraisals of this subject demonstrate that this is not the case, and there is evidence that the vast majority of students only possess basic computational skills,[7] and the general level of digital competence of children and teenagers is inadequate.[8] With respect to productivity arising from the application of digital skills, students appear to have a substantial gap when comparing activities in the lifestyle and professional areas.[9]

In designing and teaching chemical curricula to students in chemistry, biochemistry, and generally molecular life sciences, we have therefore identified the preparation of chemical drawings as an exemplary instance in this context. Molecular visualization in the context of teaching of chemical structure has been reviewed with respect to macromolecules[10-12] and appraised, mainly at the level of individual software resources, for small-molecules.[13-16] Clearly, fully capable chemical drawing software products are available, but these are predominantly provided as licensed commercial products. For example, a previous report[17] in this *Journal* illustrating the

use of Wikis for collaborative organic chemistry projects focused on two software products from commercial providers and only included JME[18] as an independently available tool. Notably, using licensed commercial software generally means additional financial costs for students. In the case of free-of-charge versions of these products, access may be limited to a short period of time and/or come with frequent advertisement and promotional activities. For one commercial product considered in this project, the advertised "academic free-of-charge" access could not be obtained at all after signing up with the software provider.

From academic groups and independent software developers, a variety of chemical drawing software is available free of charge, including standalone applications such as BKChem,[19] JChemPaint,[20] MCDL Java Chemical Structure Editor,[21] XDrawChem,[22] and others. There are also several JavaScript-based molecular editors, such as for example JSME,[23] FlameJS,[24] Ketcher,[25] and jsMolEditor,[26] that are typically designed to be embedded in web interfaces. However, from the perspective of teaching chemical structure drawings, we found limitations that impacted on concepts we find of utmost importance. For example, in many cases, the user was not provided with a number of fundamental drawing elements such as formal charges (as opposed to real charges), brackets, etc. Some of the above applications are specifically intended for embedding in web interfaces and thus lacked the convenience features of a desktop program, such as to include the copy and paste operations and access to styling features. The options and quality of image export varied between different programs, and high-resolution bitmap images sometimes required extensive efforts by the user. An additional aspect concerns the ease of installation (the dependency problem[27]), which varied for different programs, but in general required more efforts for Python-based software which, in our experience, often rendered those applications non-usable for students and/or instructors.

BACKGROUND

In an effort to address this apparent gap, we set out to develop a desktop editor for 2D chemical structures that is easy to install and deploy, and provides an intuitive graphical user interface that allows users to compose chemical drawings with a focus on generating publication-quality images, including the possibility to set the DPI resolution of exported bitmap images as well as the provision and custom-tailoring of pre-defined style settings.

In order to aid molecule import and export by means of nongraphical data, parsers and generators for molecules in formatted data files as well as line notation have been added. Whereas the generation of chemical drawings from formatted data files is straightforward as atomic coordinates are included in those data, this process is much more challenging for molecular information delivered in line notation. In order to deduce atomic coordinates from a string representation of a molecule, a procedure is required that lays out the chemical structure with sensible geometry, minimum overlap of individual components, and correct stereochemistry. In the present project, we have implemented relevant code taken from the MCDL Java Chemical Structure Editor[21] in order to generate 2D structural drawings from line notation.

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Additional convenience features include the lookup of molecular information using the NIH CADD Group Chemoinformatics Tools and User Services (CACTUS),[28] and molecule searches in the PubChem database. The graphical user interface has been translated into different languages and is currently available in English, Chinese, Farsi, French, German, Italian, Korean (Hangul), Portuguese, and Spanish. The software, manual, and video tutorials are available from the project web site.[29]

Description

The chemical drawing software cDraw has been designed as a freely available desktop application to provide students and researchers with a resource for generation of publication-quality figures and help with the teaching and learning of concepts and visualization of chemical structures. Considering the requirements for software and digital resources in teaching/learning environments, where there is a particular requirement to avoid an overload of novel techniques to be mastered, the graphical user interface (GUI) and software features have been designed to maximize intuitiveness and ease of use, so students can concentrate on understanding and applying chemical concepts when preparing chemical structure drawings. To that effect, the following features have been implemented:

Accessibility The GUI has been designed with multilanguage support and is available in nine languages.

Tutorials In addition to a comprehensive manual, video tutorials are available on the project web site[29] that illustrate the use of particular features of the software to accomplish given tasks.

Image output Drawings can be exported as EPS, PDF, PNG, SVG and TIFF images and also exported through the clipboard to other applications through copy and paste operations. The resolution of bitmap images can be set by the user through the GUI.

Styling The software has embedded style settings for American Chemical Society (ACS) and Royal Society of Chemistry (RSC), as well as the option to define and save customised styles.

Text elements can be styled and formatted conveniently using an intuitive what-you-see-is-what-you-get (WYSIWYG) text editor (see Figure 1).

2D Structure generation 2D chemical structures can be generated from line notation provided in InChI, MCDL and SMILES format.

InChI code generation InChI and InChI key can be generated directly from drawn structures.

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Chemoinformatics From drawn structures, the user can trigger the lookup of IUPAC name, general names and CAS number at the NIH CACTUS resource, as well as molecules in the PubChem database.

At present, neither the export of molecules or reactions in SMILES format nor drag and drop of molecular objects are supported. However, we plan to add these and further features in future version sof cDraw.

General Framework

The cDraw desktop chemical editor was written in Java and is distributed as a single bundled archive, thus allowing for simple and straightforward installation provided that the Java Virtual Machine is installed on the user's computer. The software builds on Java classes previously developed for our PCSB project[30] and uses JNI-InChI[31] and the MCDL editor,[21] as well as custom-designed libraries that were modeled after various modules available in the CDK.[32] Importantly, while using and building on code from other chemoinformatics projects, all required libraries are fully embedded (as opposed to included but merely linked) within cDraw in order to avoid possible dependency issues.

Conceptually, cDraw organizes the components of a chemical *Drawing* that consists of individual *ChemObjects* such as *Arrow*, *Atom*, *Bond*, and so forth. For each *ChemObject* there is a suitable *DrawingObject* (e.g., *AtomSymbol*, *SingleBond*, *DoubleBond*) that generates the 2D screen coordinates for the particular object to be drawn. The graphical rendering is handled by the class *ChemPanel*, which users interact with through the main *CDraw* class. Bitmap images are obtained as *BufferedImage*s from *ChemPanel* and then exported as PNG or TIFF files using the Java Image I/O API and Java Advanced Imaging API, respectively. For generation of Postscript and SVG images, the custom *PSgenerator* and *SVGgenerator* classes have been designed and implemented.

Chemical Data Formats

Instead of designing a new file format for storing cDraw session information, we decided to use the CDML file format as the "native" cDraw file format. CDML is an XML-based format that has previously been used by BKChem.[19] Despite several new keys needed to be added to the CDML set, we found that CDML files generated by cDraw can be successfully processed by BKChem. In order to offer exchange capabilities with other relevant software, basic import/export functionality for the ChemDraw CDXML and the CML file format[33] has also been included. Additionally, cDraw allows import of molecules provided in the popular CTfile formats SDF (SDfiles) and MOL (Molfiles); users can also export molecules generated in cDraw as SD-formatted files. Molecules can also be generated from line notation (see next section); InChI is handled by the incorporated JNI-InChI package,[31] and for processing of SMILES strings a modified version of the CDK *SmilesParser*[32] has been deployed.

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Structure Diagram Generation

Whereas the drawing of 2D molecular structures by users can in principle be achieved using graphics software without a particular chemical environment, features such as the processing of molecules in line notation require appropriate chemoinformatic capabilities. The current version of cDraw supports structure diagram generation from three different line notations: InChI; MCDL; and SMILES. Additionally, InChI and InChI Keys can be generated from 2D molecular drawings. Correct functionality of these features has been assessed using a panel of selected organic molecules of varying complexity (see the Supporting Information files).

The conversion of molecules from line notation into 2D drawings requires a module for structure diagram generation. In this context, we capitalized on the efforts by Gakh and colleagues who developed the Modular Chemical Descriptor Language (MCDL)[34,35] and a Java MCDL Chemical Structure Editor,[21] including modules for structure diagram generation. In cDraw, the user-provided line notation is parsed and then transformed in the class *StructureGenerator* into an SD-formatted representation of the molecule; stereo information such as tetrahedral chirality and double bond stereoisomerism is extracted. The SDF string is passed to MCDL for generation of structure diagram considering the required stereo configuration where applicable. From MCDL, an SDF string with atomic coordinates is obtained that is converted by *SDFparser* into a *Drawing* suitable for rendering by *ChemPanel*. Because the Kekulé form of aromatic structures is generally preferred by chemists in structure diagrams, all molecules generated from line notation are subjected to a procedure that localizes the electrons in aromatic components and assigns single and double bonds. For this reason, we have embedded relevant classes from the CDK *Kekulization* module.[32]

Styles

Scientific publications in the international, peer-reviewed journals, as well as technical reports prepared by laboratories or in educational environments, make use of particular style rules for drawing chemical structures for reasons of consistency, and to present structure representations, and reactions and schemes, in a visually appealing form. Drawing parameters such as angular increments, bond length, wedge width, and so on, therefore, need to be set to defined values. In the current version of cDraw, we have implemented the style settings for journals by the American Chemical Society (ACS) and the Royal Society of Chemistry (RSC), which can be applied by a simple selection from the style menu. For customized styles, users can also define their own style settings and save into/load from external style files.

NIH CACTUS and PubChem Queries

For molecules generated with cDraw, users can obtain information, such as the Chemical Abstract Service (CAS) registry number, IUPAC name, or general names, using queries to the Chemical Identifier Resolver of the NIH CADD Group Chemoinformatics Tools and User Services (CACTUS).[28] The cDraw drawing is analyzed for individual molecules, for which an InChI string is calculated. The InChI is then submitted to NIH CACTUS in the user-selected query.

Internationalization and Convenience

Intuitive graphical user interfaces are generally deemed to be designed such that users are able to accomplish a certain task effectively, building—unconsciously—on their previous knowledge. The previous knowledge results from prior—conscious—learning activities; repeated practice turns this knowledge into operations that can be mastered without considering them.[32] The cDraw graphical user interface has thus been designed with careful consideration of (assumed) general knowledge of users with regards to desktop software (menu items, action buttons) as well as drawing operations. Mnemonics and accelerator keys used by other popular desktop software have been implemented, and tooltips are available for all action buttons and specialized menu items to make the learning experience as convenient and straightforward as possible. A WYSIWYG text editor has been designed and implemented to afford text input in a straightforward fashion (Figure 1). As the cultural environment of student/nonprofessional users of software of this kind varies widely, cDraw has been designed with multilanguage support and the current version is available in nine languages: English, Chinese, Farsi, French, German, Italian, Korean, Portuguese, and Spanish. Video tutorials demonstrating basic operations when drawing chemical structures with cDraw are available on the project home page.[29]

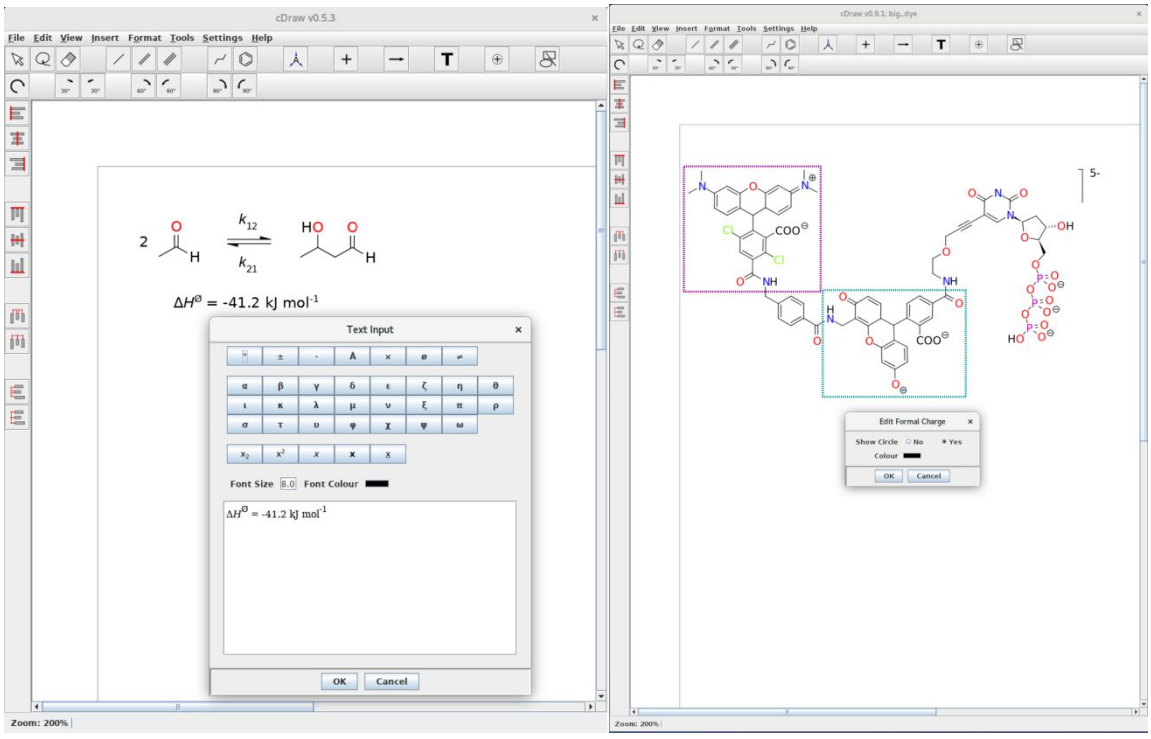

Figure 1. Screenshots of the cDraw graphical user interface. Left: Use of the text editor. A left button mouse click brings up the **Text Input** dialog where text can be entered and formatted with a WYSIWYG editor. Special characters and Greek characters can be inserted using the provided buttons. A set of formatting options for characters is also available by means of provided buttons. Font size and font color can be also changed, but these settings apply to the entire text object. The line spacing can be set in **Miscellaneous Settings** from the **Settings** menu. Right: Drawing of one of the four BigDye™ terminators, ddT-EO-6CFB-dTMR. Automatic atom colouring has been selected (**Colour** from the **Settings** menu); note that the carboxyl groups are treated as labels and thus appear in uniform colour. The half bracket and formal charges were inserted directly as individual objects from the **miscellaneous drawing features**. A right button mouse click on one of the charges brings up the styling menu for formal charges.

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EXAMPLES OF USE

cDraw allows generation of chemical structure diagrams and reaction schemes in an easy and intuitive fashion; high-resolution images of molecules and reaction schemes can be readily embedded in documents such as articles and assignments, but also on posters and web sites. Export of drawings as SVG allows for further graphical modification with vector graphics software such as Inkscape.[37]

The use of fundamental drawing operations and features is demonstrated in video tutorials available on the project web site,[29] and currently includes an introduction of basic drawing operations and detailed illustrations of drawing bonds, editing atoms as well as the drawing of a Retro-Diels-Alder reaction demonstrating the use of arc arrows, brackets and charges. cDraw has been downloaded by >350 users worldwide since its first release in February 2018, and we have used the software in a second-year organic chemistry course that is taken by students from diverse ethnic backgrounds. Students used the software on a range of operating systems to prepare experiment protocols and laboratory reports. Our experience showed that the software was mastered quickly and enabled the inclusion of publication-quality figures in students' work.

Beyond the mere technical capability, we believe that this project contributes to an in-depth approach that frequently plays an underrated role in modern educational institutions. The availability and usage of free software for educational activities at all levels, including the STEM disciplines, promotes to students the values of independence, cooperation, and capability. The ability to freely use, and ultimately examine the methods used is akin to the free availability of scientific literature with all the benefits that entails.[38]

CONCLUSION

The chemical drawing software cDraw is a standalone interactive desktop tool for generation and 2D chemical structures and reaction schemes that provides the fundamental chemical graphics elements and allows straightforward and quick generation of chemical diagrams in the most popular image formats. Because it has no other dependency than the Java virtual machine, it is conveniently deployed across different platforms. Its intuitive graphical user interface and support of different language environments makes the software particularly suitable for educational environments.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications web site at DOI: 10.1021/acs.jchemed.XXXXXXX.

Structure generation from SMILES (PDF)
Structure generation from InChI (PDF)
Generation of InChI from drawn structure (PDF)
Deployment of cDraw in teaching and educational contexts (PDF)

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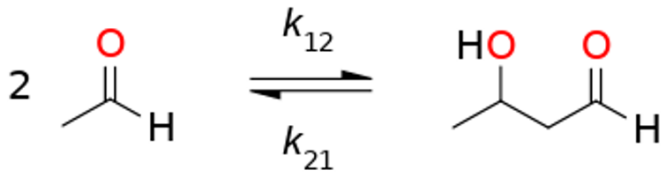

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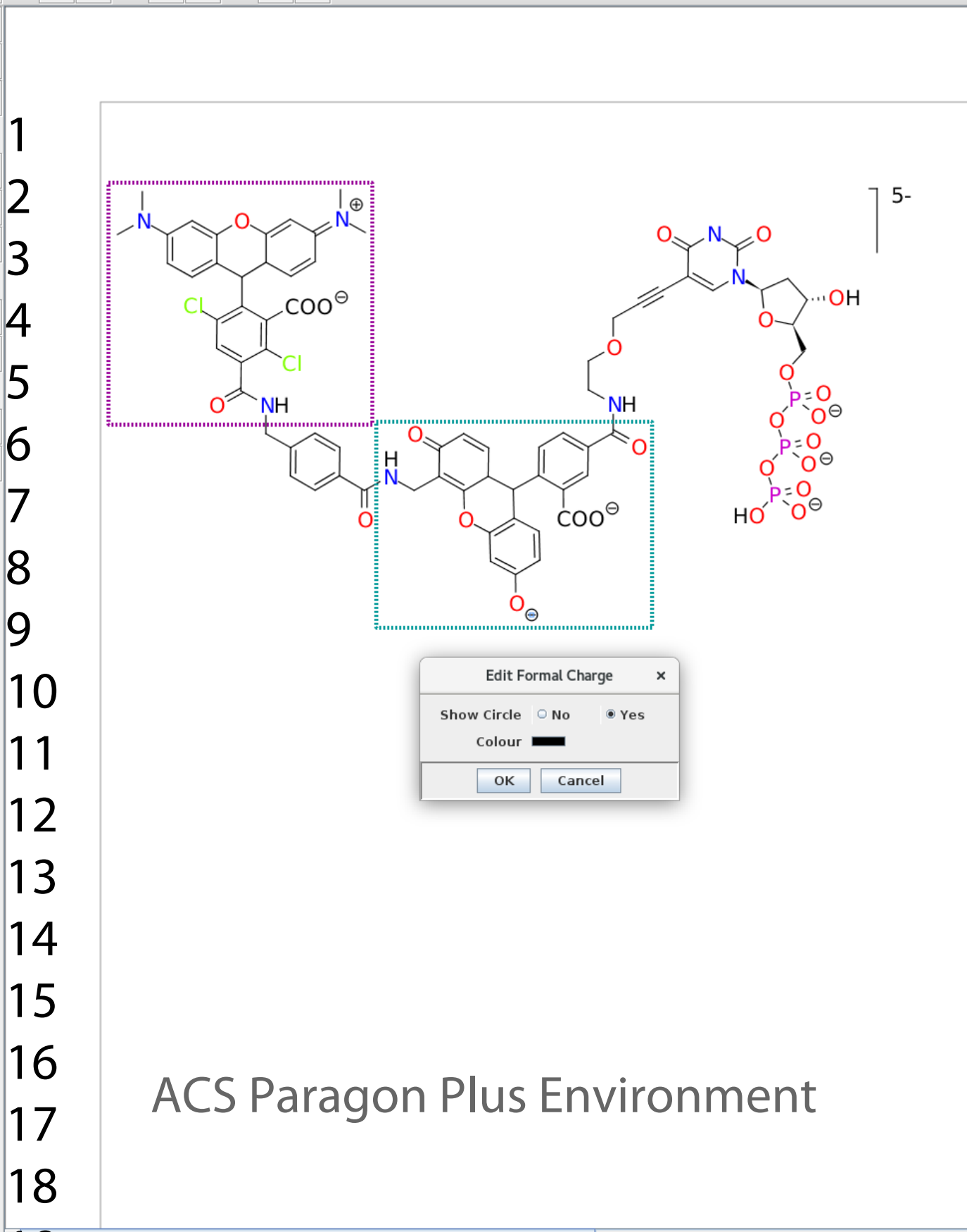
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